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HELLER EHRMAN LLP
275 MIDDLEFIELD ROAD
MENLO PARK, CA 94025-3506

EXAMINER	
O HARA, EILEEN B	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 02/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/978,191	GODDARD ET AL.	
	Examiner	Art Unit	
	Eileen B. O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58-63,69 and 70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58-63,69 and 70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims

1. Claims 58-63, 69 and 70 are pending in the instant application. Claims 58-62 have been amended as requested by Applicant in the Amendment filed November 18, 2005.

Withdrawn Objections and Rejections

2.1 Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

2.2 Upon further consideration the rejections under 35 U.S.C. 102(b) and 35 U.S.C. 103(a) have been withdrawn, since this application is a direct continuation of 09/040,220, and is accorded an effective priority date of March 17, 1998.

Maintained Rejections

Claim Rejections - 35 USC § 101 and § 112

35 U.S.C. 101 and 112, first paragraphs read as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.
>
> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 58-63, 69 and 70 remain rejected under 35 U.S.C. 101 and 112, first paragraph, because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, for reasons of record in the previous office actions, mailed June 2, 2004, at pages 5-9, March 16, 2005 at pages 3-10, Sept. 20, 2005 and below.

Claims 58-63, 69 and 70 also remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicants' arguments (pages 4-20, Paper filed November 18, 2005) have been fully considered but are not fond to be persuasive for the following reasons.

Applicant argues at pages 4-8 of the response that the gene amplification assay is well-described in Example 114, showing that nucleic acids encoding PRO213-1 were significantly overexpressed in certain cancers such as colon, lung breast and other tumors as compared to the normal control, providing a patentable utility for the nucleic acids encoding PRO213-1 and their variants. The Examiner agrees with Applicants that the nucleic acids have utility as a diagnostic of lung cancer, however, the instant invention is drawn to polypeptides encoded by the nucleic acid, and because the art teaches that there is not necessarily a correlation between amplified genomic DNA and mRNA, or mRNA and encoded protein, the polypeptides do not have either a specific and substantial asserted utility or a well established utility.

Applicants at pages 8-9 refer to the Gygi et al. and Pennica et al. references. Applicants submit that the teachings of Pennica et al. are specific to WISP genes, and say nothing about the correlation of gene amplification and protein expression in general. Specifically, Pennica et al. (1998, PNAS USA 95:14717-14722), show a lack of correlation between gene amplification and overexpression in two out of three WISP genes. Hyman (Cancer Research 62:6240-6245, of record) found 44% of *highly* amplified genes showed overexpression at the mRNA level, and 10.5% of *highly* overexpressed genes were amplified; thus, even at the level of high

amplification and high overexpression, the two do not necessarily correlate. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the slight amplification of PRO213-1 would be correlated with elevated levels of mRNA, much less protein. Hyman does not examine protein expression.

Applicants submit that Gygi et al. supports Applicants position that there is a positive correlation between mRNA levels and protein levels. While Gygi et al. demonstrates that high levels of mRNA generally correlate with high levels of protein and that it appears that there is a general positive correlation between mRNA levels and protein levels, it has not been demonstrated that the PRO213-1 mRNA is over-expressed.

Applicants on page 9 of the response assert that Lian et al. only teach that protein expression may not correlate with mRNA level in differentiating myeloid cells and does not teach anything regarding such a lack of correlation for genes in general, and that myeloid cell differentiation relates to hematopoiesis and is an entirely different biological process from solid tumor development because these two processes involve entirely different regulatory mechanisms and molecules. Applicants' arguments have been fully considered but are not deemed persuasive. Applicants have not provided any references demonstrating that the myeloid cells and solid tumors involve entirely different regulatory mechanisms and molecules. Additionally, Applicants use Gygi et al. to support their position, but the data in Gygi et al. was obtained from yeast, which one of ordinary skill in the art would consider far more different from lung tumor than myeloid cells.

Applicants submit that the authors themselves admit that there are a number of problems with the data presented in this reference, that membrane and other hydrophobic proteins and very basic proteins are not well displayed by the standard 2DE approach, and proteins present at low levels will be missed, and in addition, Coomassie dye stain was used rather than silver, which decreases the sensitivity of the detection of minor proteins. The authors admit to such limitations, but by publishing the data they apparently feel the data is useful to the public.

Applicants on pages 9-10 criticize Feller et al. as only examining the expression level of a few proteins/RNAs in response to LPS stimulation, which involves an entirely different regulatory mechanism from that involved in tumor development, and therefore do not apply here, and the PTO has overlooked a number of limitations of the study by Fessler et al (page 10 of the response).

Applicants' arguments have been fully considered but are not deemed persuasive. Applicants have not provided any references demonstrating that the neutrophils of Fessler and solid tumors involve entirely different regulatory mechanisms and molecules. Additionally, Applicants use Gygi et al. to support their position, but the data in Gygi et al. was obtained from yeast, which one of ordinary skill in the art would consider far more different from lung tumor than neutrophils. Fessler et al. expressly detail the limitations of their study on page 31301, first column. Additionally, both Lian and Fessler, working in this field, characterize Gygi et al. as showing that there is not a good or a poor correlation between mRNA and protein levels (Lian, page 513, second column, Fessler, page 31291, last paragraph.

Applicant criticizes Chen et al. as not being applicable to the present application. Applicant asserts that Chen et al. only studied proteins detectable by 2D gels, and characterizes

Haynes et al. as being critical of selecting proteins detectable by 2D gels, and quotes from Haynes et al. "It is apparent that without prior enrichment only a relatively small and highly selected population of long-lived, highly expressed proteins is observed. There are many more proteins in a given cell which are not visualized by such methods. Frequently it is the low abundance proteins that execute key regulatory functions" (Haynes, p. 1870, col. 1). This has been considered but not found persuasive. While Haynes et al. identifies limitations of this method of protein analysis, Haynes et al. also used the same method, 2D gels and mass spectrometry, to obtain their data, and discuss the advantages of this method. On page 1864, second column, Haynes et al. states "There is considerable interest in developing a proteome analysis strategy which bypasses 2-DE altogether, because it is considered a relatively slow and tedious process, and because of the perceived difficulties in extracting proteins from the gel matrix for analysis. However, 2-DE as a starting point for proteome analysis has many advantages compared to other techniques available today. The most significant strengths of the 2-DE-MS approach include the relatively uniform behaviour of proteins in gels, the ability to quantify spots and the high resolution and simultaneous display of hundreds to thousands of proteins within a reasonable time frame." Haynes et al. on page 1870, first column, states "Comparative analysis of 2-DE protein patterns is therefore ideally suited for the detection, identification and analysis of suitable markers." And while Haynes et al. showed that there was a strong correlation between the most highly expressed proteins and mRNA levels using this same method, this was not the result in Chen et al. Chen et al. additionally did a detailed analysis of separate subsets of proteins with differing levels of abundance, and also showed a lack of

correlation between mRNA and protein expression among the 165 protein spots (page 310, column 1).

Applicant also criticizes Chen et al. for looking at expression levels across a set of samples including a large number of samples (76) along with a much smaller number of normal samples (9), and for determining the relationship between mRNA and protein expression by using the average expression values for all samples, and therefore did not account for different expression in different tissues or different stages of cancer. This has been considered but not found persuasive. Applicant is holding Chen at al. to a higher standard than that of the instant application, in which there is no information on how many samples were tested, no information about type or stage of tumour, no comparison with the equivalent normal tissue, and no information on protein level.

Thirdly, Applicants submit that no attempt was made to compare expression levels in normal versus tumour samples, and that the authors concede that they had too few samples for meaningful analysis (Chen, p.310, col. 2). Applicant asserts that as a result, the analysis in the Chen paper shows only that a number of randomly selected proteins have varying degrees of correlation between mRNA and protein expression levels within a set of different lung adenocarcinoma samples, and the Chen paper does not address the issue of whether increased mRNA levels in the tumour samples taken together as one group, as compared to the normal samples as a group, correlated with increased protein levels in tumour tissue versus normal tissue.

This has been considered but not found persuasive. The section in Chen referred to did not refer to the entire sample, but addressed determining whether the 21 genes showing a significant

correlation between the protein and mRNA expression among all samples demonstrate changes in this relationship during tumour progression, and the correlations were examined separately for stage I (n=57) and stage III (n=9) lung adenocarcinomas. The number of non-neoplastic lung samples (n=9) was insufficient for a separate correlation analysis of this group. Again, Applicant is holding Chen at al. to a higher standard than that of the instant application, in which there is no information on how many samples were tested, no information about type or stage of tumour, no comparison with the equivalent normal tissue, and no information on protein level.

Applicant asserts that the correct test of utility is whether the utility is "more likely than not", and assert that Chen et al. Table 1 shows that 40 genes out of 66 had a positive correlation between mRNA and protein expression, and that in Table II, 30 genes with multiple isoforms were presented, in which for 22 out of 30, at least one isoform showed a positive correlation between mRNA expression and protein expression. Applicants submit that 12 genes out of 29 showed a strong positive correlation for at least one isoform, no genes showed a significant negative correlation, and certain isoforms are likely non-functional proteins. Thus, Table II also provides that it is more likely than not that protein levels will correlate with mRNA expression levels.

This has been considered but not found persuasive. In Table I, only 9 out of the 66 genes listed had a statistically significant positive correlation. For Table II, 19 out of 96 protein spots showed a statistically significant correlation between protein and mRNA expression. And though 12 genes out of 29 showed a strong positive correlation for at least one isoform, that is only 41%. Additionally, there is no information on which isoforms would be functional proteins

and therefore no correlation between abundance of mRNA, protein level and functionality of protein.

Applicant submit the Beer et al. paper, having the same authors as in Chen et al., in which the authors look at several survival associated genes from lung adenocarcinoma, and report that the genes are expressed at the protein level and demonstrate similar mRNA and protein-expression patterns (page 822, col.1). Although the paper found a positive correlation between mRNA and protein expression, only 10 genes were analyzed. Additionally, these ten genes were selected for analysis because they were associated with survival and were highly expressed. The art indicates that highly expressed mRNAs correlate with high protein expression. However, there is no information in the instant application that the PRO213-1 mRNA is highly expressed. There are many papers that demonstrate no or little correlation, as discussed above and below. A review of the literature indicates that some references demonstrate a positive correlation between mRNA expression and protein levels, while some show no correlation. From this, one of ordinary skill in the art would not assume that if an mRNA were differentially expressed, the protein would also be expressed in a corresponding manner.

Applicants further submit that the Orntoft, Hyman and Pollack references indicate that it is more likely than not that increased gene expression levels correlate with increased expression of the protein. This has been fully considered but is not found to be persuasive.

Applicants submit on page 12-13 of the response that the teachings of Anderson et al. do not apply to the presently claimed invention because Anderson et al. studied mRNA/protein correlation in proteins obtained from liver tissue, while the present invention is directed to

polypeptides that are overexpressed in lung and colon tumor, which is an entirely different cellular environment from liver tissue, and it would be apparent that different post-translational or post-transcriptional regulation mechanisms are involved in these two systems. Applicants' arguments have been fully considered but are not deemed persuasive. Applicants have presented no evidence that the post-translational or post-transcriptional regulation mechanisms differ from lung tumor and liver tissue. Additionally, Applicants use Gygi et al. to support their position, but the data in Gygi et al. was obtained from yeast, which one of ordinary skill in the art would consider far more different from lung tumor than liver cells. Applicants further submit that Anderson admitted that several experimental flaws in this paper will limit the accuracy of the data. Anderson et al. addresses this on page 536, right column, and states:

"Although the measurements obtained show good (low) standard deviations across a set of six individual livers, it is well known that different proteins can bind CBB with different affinities. Thus the measurement scale for one protein may differ from another by up to approximately twofold. Since, however, these relative scale errors should be normally distributed, we expect them to have little effect on the overall correlation. Precision of the mRNA measurements is also limited, in this case because a limited number of clones was detected for the selected proteins. Five genes, for example, were represented by only one clone each among the 7925 clones sequenced from the respective CDNA tissue libraries. This low relative expression at the mRNA level is expected since a majority of the high abundance mRNAS in liver code for plasma proteins. However, such small numbers of clones lead to potentially large quantitative errors because of sampling error. Here again, we believe these errors should be relatively random across the set of proteins chosen, and thus should not skew the result appreciably. A third potential difficulty is that the databases used for the protein and mRNA abundance estimates were prepared from different samples. In future, it will thus be of great interest to repeat the experiment using the same samples to examine both mRNA and protein abundances."

Therefore, Anderson et al. believe their data is relatively accurate. Applicants further submit that Anderson et al. supports their position by showing a correlation of 0.48. Anderson et al. address this on page 536, right hand column:

"Matches were found for 19 proteins, and the correlation coefficient obtained over this set of data was 0.48. This number is intriguingly close to the middle position between a perfect correlation (1.0) and no correlation whatever (0.0). One simple interpretation of such a value is that the two major phases of gene expression regulation (transcription through message degradation on the one hand, and translation through protein degradation on the other) are of approximately equal importance in determining the net output of functional gene product (protein)."

Though Anderson et al. found some correlation with this data set, they reanalyzed an analogous set of data for plasma proteins secreted by the liver published by Kawamoto et al. On page 536, left column, Anderson et al. states:

"An analogous set of data for plasma proteins secreted by the liver has been published by Kawamoto et al. [12] and we have reanalyzed their values to see whether a similar mRNA-to-protein relationship holds. It appears, based on nine plasma proteins, that a higher correlation coefficient applies: 0.96. This result is less convincing, however, because one gene product (albumin) is well-separated from the cluster of the remaining eight, and thus exercises a disproportionate influence on the correlation coefficient. In fact, if albumin is omitted from the calculation, the correlation coefficient is reduced to -0.19, which suggests a very poor correlation."

Therefore, from the Anderson et al. paper alone, one of ordinary skill in the art would not assume that if an mRNA were overexpressed, the protein would correspondingly be overexpressed.

Applicants reiterate that the evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. Applicants submit that the Office has failed to meet its initial burden of proof that Applicant's claims of utility are not substantial or credible, and that the arguments presented by the Examiner in combination with the Fessler, Lian, Chen et al. and Anderson et al. papers do not provide sufficient reasons to doubt the statements by Applicants that PRO213-1 has utility, and that the papers support Applicant's position. Applicants' arguments have been fully considered but are not deemed persuasive, for the reasons discussed above. While the credibility of the utility is not in doubt, based on the totality of the art, the asserted utility is not considered substantial.

At pages 14-16 of the response, Applicant refers to Orntoft et al., Hyman et al., and Pollack et al. collectively teach that in general, gene amplification increases mRNA expression, and the Declaration of Dr. Paul Polakis shows that in general, there is a correlation between mRNA levels and polypeptide levels.

Applicant discusses Orntoft et al. (Molecular and Cellular Proteomics 1:37-45, 2002), in which the 40 proteins Orntoft et al. looked at did show a clear correlation between mRNA and protein expression levels. However, as discussed previously, only abundant proteins were analyzed, and the art indicates that very abundant transcripts correlated with high protein levels.

Applicants on pages 14-15 of the response state that the Examiner also appears to misunderstand the data presented by Hyman et al., and that the significant figure is not the percentage of genes that show amplification, but the percentage of amplified genes that demonstrate increased mRNA and protein expression. Applicants' arguments have been fully

considered but are not deemed persuasive. While almost half (44%) of the highly amplified genes showed overexpression of transcript, more than half did not. Therefore, from Hyman et al., there is not a more likely chance than not that an amplified gene results in overexpressed transcript.

At pages 15-16 of the response, Applicant refers to Orntoft et al., Hyman et al., and Pollack et al. collectively teach that in general, gene amplification increases mRNA expression, and the Declaration of Dr. Paul Polakis shows that in general, there is a correlation between mRNA levels and polypeptide levels. Applicants submit that the PTO has failed to provide evidence demonstrating a lack of correlation between gene amplification and increased mRNA and protein levels, in general, that that Dr. Polakis' statement that "an increased level of mRNA in a tumour cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumour cell relative to the normal cell" is based on factual experimental findings, clearly set forth in the Declaration, and the Office Action's suggestion that Dr. Polakis might be misrepresenting these experimental results out of an interest in the outcome of the case is inappropriate. Applicants' arguments have been fully considered but are not deemed persuasive. Although Dr. Polakis may have found a correlation of 80% between overexpressed transcripts and overexpressed protein, some references cited demonstrate a correlation, while others do not, so that it is not predictable from the art that overexpressed transcript correlates with overexpressed protein.

Applicants assert that taken together, although there are some examples in the scientific art that do not fit with the central dogma in molecular biology that there is a correlation between polypeptide and mRNA levels, these instances are exceptions rather than the rule, and in the

majority of cases of amplified genes, the teachings in the art, as exemplified by Orntoft et al., Hyman et al., Pollack et al., and the Polakis Declaration, overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO213-1 gene, that the PRO213-1 polypeptide is concomitantly overexpressed, and thus the polypeptides have utility in the diagnosis of cancer.

At page 17 of the response Applicants submit that Hu et al. does not conclusively show that it is more likely than not that gene amplification does not result in increased expression at the mRNA and protein levels, and that Hu et al. manipulated various aspects of the input data to reduce the false positive rate and therefore under-represented some genes, and submit that the statistical analysis by Hu et al. is not a reliable standard because the frequency of citation only reflects the current research of interest of a molecule but not the true biological function of the molecule. Finally, the conclusion in Hu et al. only applies to a specific type of breast tumor (estrogen receptor (ERl-positive breast tumor) and can not be generalized as a principle governing microarray study of breast cancer in general, let alone the various other types of cancer genes in general. In fact, even Hu et al. admit that "(i)t is likely that this threshold will change depending on the disease as well as the experiment. interestingly, the observed correlation was only found among ER-positive (breast) tumors not ER-negative tumors." (See page 412, left column). Therefore, based on these findings, the authors add, "This may reflect a bias in the literature to study the more prevalent type of tumor in the population. Furthermore, this emphasizes that caution must be taken when interpreting experiments that may contain subpopulations that behave very differently." (Id.; emphasis added). Applicants note that they do

not argue that Hu et al. lacks reproducibility, standard error rates, etc. for their data, given that Hu et al. did a literature survey and conducted no actual experiments of their own. Rather, Applicants' point is that, given the various biases in selecting the data to be considered, as acknowledged by the authors themselves, the collection of data surveyed by Hu et al. simply does not demonstrate the conclusion the PTO attempts to reach concerning a general lack of correlation between microarray data and biological significance. Accordingly, Applicants respectfully submit that the Examiner has not shown a lack of correlation between microarray data and the biological significance of cancer genes.

Applicants' arguments have been fully considered but are not deemed persuasive, for reasons of record in the previous office action.

Applicants on page 18 submit that Hanna et al. supports Applicants' position, in which Hanna et al. state that in general, FISH and IHC results correlated well. Applicants' arguments have been fully considered but are not deemed persuasive. For this one particular gene, FISH and IHC results may correlate well, but it is not predictable that other genes would have the same correlation.

Applicant submits that similar to the HER-2/neu gene disclosed in Hanna et al., the PRO213-1 gene is a tumor associated gene, since the PRO213-1 gene is amplified in at least 35 primary lung and colon tumors and lung and colon cell lines, and that one of skill in the art would reasonably expect that the polypeptide is concomitantly overexpressed. However, as discussed in the previous office actions and supra, the preponderance of the art does not support that is it more likely than not that gene amplification results in greater mRNA and protein levels.

Applicant points to the declaration of Dr.. Ashkenazi, submitted under 37 CFR 1.132 on

04 October 2004, as establishing that, even is the protein were not over-expressed, the simultaneous testing of gene amplification and gene product over-expression would enable more accurate tumor classification. However, while this may be true, the specification does not disclose such further testing of gene product over-expression. Therefore, the skilled artisan would have been required to do the testing. In view of such requirement, the products or services based on the claimed invention are not in "currently available" form for the public. On page 19 of the response, points out that the variants of SEQ ID NO: 506 whose encoding nucleic acids are not amplified in lung tumors are not encompassed by the claims.

Applicant concludes that the present rejection is based on the application of an incorrect, elevated legal standard, on misconstruction of the references and erroneous conclusions drawn therefrom, and that the issue of patentable utility should be assessed on the totality of evidence, using the preponderance evidentiary standard. It is submitted that on the totality of evidence Applicants clearly established that the claimed invention has a substantial, specific and credible utility. Further, based on this utility and the disclosure in the specification, one skilled in the art at the time the application was filed would know how to use the claimed polypeptides.

This has been fully considered but is not found to be persuasive. This asserted utility is not substantial, since the specification does not provide a clear nexus between PRO213-1 and cancer occurrence or progression, for reasons noted above. Furthermore, the evidence of record clearly indicates that an increase in gene amplification does not correlate well with protein over-expression, for reasons noted above in the discussions of the individual references. Thus, the preponderance of the art supports the *prima facie* finding that an amplification of DNA would

not form the basis for a substantial assertion of an association between PRO213-1 protein and cancer.

4. Claims 58-62, 69 and 70 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis of this rejection is set forth at pp. 9-10 of the Office Action mailed 02 February 2004 and pages 11-13 of the Office Action mailed 16 March 2005 and the Office Action mailed Sept. 20, 2005.

Applicants traverse the rejection on pages 20-22 and assert that the polypeptide comprising the sequence set forth in SEQ ID NO: 506 meets the written description requirement of 35 U.S.C. 112, first paragraph, and thus the genus of polypeptides with at least 80% sequence identity to SEQ ID NO: 506, which possess the functional property of having a nucleic acid which is amplified in lung tumors would meet the requirement of 35 U.S.C. 112, first paragraph, as providing adequate written description. Applicants assert that the present application also describes methods for identifying genes which are amplified in lung cancer, and that by following the disclosure in the specification, one skilled in the art can easily test whether a gene encoding a variant PRO213-1 protein is amplified in lung cancer, and also the specification further describes methods for the determination of percent identity between two amino acid sequences.

Applicants assert that an applicant may also show that an invention is complete by disclosure of sufficiently detailed relevant identifying characteristics which provide evidence that

applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. Applicants submit that they have recited structural features, namely, 80% sequence identity to the genus of claimed polypeptides is further defined by having a specific functional activity for the encoding nucleic acid, of being amplified in lung tumors. Applicants also direct the Examiner's attention Example 14 of the Synopsis of Application of Written Description Guidelines issued by the U.S. Patent Office, which clearly states that protein variants meet the requirements of 35 U.S.C. 112, first paragraph, as providing adequate written description for the claimed invention even if the specification contemplates but does pot exemplify variants of the protein if (1) the procedures for making such variant proteins are routine in the art, (2) the specification provides an assay for detecting the functional activity of the protein and (3) the variant proteins possess the specified functional activity and at least 95% (80%) sequence identity to the reference sequence.

Applicants' arguments have been fully considered but are not deemed persuasive. In this case, the only factors present in the claim are functional, in that the protein of SEQ ID NO: 506 is encoded by a nucleic acid that is amplified in lung cancer. The specification discloses only a single sequence, SEQ ID NO: 506, that meets the limitations of the claims. It is clear that while there *could* be additional polypeptides that meet the limitations of the claims, that conception of such polypeptides has not occurred, and cannot occur until their actual isolation, as it is not predictable what additional mutations in SEQ ID NO: 506 would occur in nature and further be amplified in lung cancer. As previously stated, one cannot describe what

one has not conceived. See *Fiddes v. Baird*, 30 USPQZII 1481 at 1483. In *Fiddes,* claims directed to mammalian FGF'S were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. In this case, applicants have described a single sequence asserted to be associated with lung cancer, and propose to obtain coverage for all related sequences that have a similar association. There is no description of that class of compounds. This case is also analogous to that in *Amgen v. Chugai*, 18 USPQ 2d 1017 (1991), in which it was found that conception may not be achieved until reduction to practice in cases involving cloning genes. In this case, applicants have no conception of which of the thousands of possible polypeptides and nucleic acids that could encode the protein of SEQ ID NO: 506 would meet the limitation of being amplified in lung cancer.

Vas-cath Inc. v. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. Chugai Pharmaceutical Co. L td.*, 18 USPQ2d 1016.

Therefore, polypeptides comprising the sequence set forth in SEQ ID NO: 506, but not the full breadth of the claims meet the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

It is believed that all pertinent arguments have been answered.

Conclusion

5. No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached at (571) 272-0961.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://portal.uspto.gov/external/portal/pair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Eileen B. O'Hara, Ph.D.

Patent Examiner

EILEEN B. O'HARA
PATENT EXAMINER